The claimed invention is directed to polynucleotides having a sequence selected from the group consisting of SEQ ID NOS:1-7, to methods of detecting a target polynucleotide using the polynucleotides of SEQ ID NOS: 1-7 and to kits comprising these polynucleotides.

As discussed in Example 1 on page 54, EST's corresponding to the consensus sequence of BS274 were found in 23.0% (9 of 39) of breast tissue libraries. EST's corresponding to the consensus sequence SEQUENCE ID NO: 7 (or fragments thereof) were found in only 0.8% (6 of 739) of the other, non-breast, libraries of the data base. Therefore, the consensus sequence or fragment thereof was found more than 28 times more often in breast than non-breast tissues.

As discussed in the specification beginning on page 3, there is a need in the art for the identification of new markers that can be used in the diagnosis, monitoring and treatment of patients suffering from breast disease, particularly, breast cancer. For example, the identification of new markers can be used in the management of breast disease. More specifically, such markers could be used to monitor for the elevated expression of such markers in inappropriate body compartments (i.e, outside of their normal host tissue, the breast) (See, specification, page 3, lines 15-18). The identification of such expression outside the normal host tissue would indicate breast disease. Examples of other well-known markers that are used in a similar manner are prostate specific antigen (PSA) and carcinoembryonic antigen (CEA). PSA is normally secreted at high levels into the seminal fluid and is present in very low levels in the blood of men with normal prostates. However, in patients with diseases of the prostate, including benign prostatic hyperplasia (BPH) or adenocarcinoma of the prostate, the level of PSA is markedly elevated in the blood and is a strong indication of disease of the prostate.

Similarly, CEA is a normal component of the inner lining of the colon and is present stool and in blood at low levels in people without disease of the colon. However,

in disease of the colon, including inflammatory bowel disease and adenocarcinoma of the colon, the concentration of CEA is markedly elevated in the blood plasma or serum of many patients and is an indicator of disease of that tissue (such as colorectal cancer).

Additionally, like BS274, PSA and CEA are expressed in a few tissues other than the colon and prostate. Nonetheless, these markers are still recognized as useful in the diagnosis of disease of their primary tissue of origin due to their strong tissue selectivity.

In the Office Action, the Examiner states the data provided "only demonstrates that BS274 is a breast specific marker." Applicants submit that tissue specific markers are very useful and in fact, possess a number of utilities. PSA is the most prominent tissue-specific marker used in medical diagnosis today.

One important utility of tissue-specific markers is shown in Figure 1 that was submitted with Applicants last Amendment. Figure 1 is the result of a RT-PCR assay designed to demonstrate the utility of BS274 as a marker that can help to identify a Tumor of Unknown Primary Origin. Tumors (cancers) of unknown origin (also known as cancers of unknown primary site) are unfortunately a huge medical problem. The exact incidence of these tumors/cancers is unknown, because many of these patients are "assigned" other diagnoses and are not represented accurately in tumor registries. (See *Cancer Principles & Practices of Oncology,* Lippincott Williams & Wilkins, page 2537). It is believed that cancers of unknown origin accounted for 2% of all cancer diagnoses reported by Surveillance, Epidemiology and End Results registries between 1973 and 1987. *Id.* Some scientists, however, believe that a more realistic estimate of the incidence of these patients is 6% of all invasive cancers in the United States per year (approximately 80,000 to 90,000 patients). It is important for the clinical physician to identify the origin of such tumors/cancers in order to develop an appropriate treatment regimen for the patient. This is important because over the last few decades, several important oncologic issues have changed. *Id.* Combination chemotherapy, often used

with surgery or radiation therapy, have proved to be potentially curative for selected patients with several metastatic tumors. *Id.* In addition, palliation and prolongation of survival have been demonstrated after systemic therapy for patients with many other tumor types. *Id.* Furthermore, treatment continues to evolve and improve. *Id.* Such therapeutic improvements have relevance for patients with tumors/cancers of unknown origin, because some have responsive neoplasms. *Id.* Therefore, there is a need in the art for new markers that can be used to identify such tumors/cancers of unknown origin. Thereupon, as shown in the explanation of Figure 1 provided below, BS274 is a marker that is clearly able to determine the origin of a tumor of unknown origin that has metastasized, specifically, that the tumor originated from the breast.

In order to provide the data for Figure 1, reverse transcriptase-polymerase chain reaction (RT-PCR) was performed. In Figure 1, lane 1 shows a 100 bp MW marker set. Lane 2 is a genomic DNA negative control. Figure 1 shows a 140 bp BS274-specific PCR amplification product in lanes 3 and 7. Lanes 3 and 7 are breast tumor and breast cancer cell line T47D respectively. The human genomic DNA control (lane 2) did not yield a 140 bp amplicon, suggesting that the 140 bp amplicons observed in 3 and 7 were the result of amplification of mRNA and not DNA. The expression of BS274 is minimal or absent in other tumor types. These results illustrate the specificity of BS274 for breast cancer tissues. In fact, this data strongly supports that BS274 could be used as a marker to establish the origin of a tumor of unknown primary origin. In addition to the above utility, BS274 could also be used to detect disease in the blood, much like PSA. As shown in Figure 1, the 140 bp BS274 band is not present in the cDNA from peripheral blood lymphocytes (PBL, lane 8). This supports the utility of BS274 as a tumor cell detection marker. If, for example, BS274 were found to be present in isolated fractions of peripheral blood, obtained from a patient, it would be attributed to the presence of breast cells since the expression of BS274 is not seen in normal PBL's. Since under normal conditions breast cells are not shed into the blood, the presence of them indicates the organ has become diseased.

35 U.S.C. Section 101 has two purposes. First, 35 U.S.C. Section 101 defines the categories of inventions that are eligible for patent protection. An invention that is not a machine, an article of manufacture, a composition or a process cannot be patented. Second, 35 U.S.C. Section 101 serves to ensure that patents are granted on only those inventions that are "useful". *Manual of Patent Examining Procedure* Section 2107.01 (8th Edition, August 2001). Therefore, to satisfy the requirements of 35 U.S.C. Section 101, an applicant must claim an invention that is statutory subject matter and must show that the claimed invention is "useful" for some purpose, either explicitly or implicitly. *Id.*

To be "useful" for some purpose, the invention must have a specific and substantial utility (i.e. "a practical utility"). A "specific" utility is specific to the subject matter claimed (versus a "general utility" that would be applicable to a broad class of invention). A "substantial utility" defines a "real world" use. Not only must the invention have a specific and substantial utility, but this utility must be credible. Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record (e.g. test data, affidavits or declarations from experts in the art, patents or printed publications). *Manual of Patent Examining Procedure* Section 2107 (8th Edition, August 2001). An applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement. *Id.*

To properly reject a claimed invention under 35 U.S.C. Section 101, the Examiner must (a) make a *prima facie* showing that the claimed invention lacks utility, and (b) provide a sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing (*Manual of Patent Examining Procedure* Section 2107.02 (8th Edition, August 2001)). The Examiner must do more than question the operability of the invention. Specifically, the Examiner must set forth factual reasons that would lead one skilled in the art to question the objective truth of the statement of operability. *Id.* In view of the previously submitted data, Applicants submit that the Examiner has failed to set forth factual reasons that would lead one skilled in the art to question the objective truth of the statement of operability of the present invention as discussed herein.

In view of the above arguments and the evidence presented in previous Amendments, Applicants respectfully submit that the Examiner has failed to make a *prima facie* showing that the claimed invention lacks utility. However, even assuming *arguendo* that the Examiner has made a *prima facie* showing that the claimed invention lacks utility, the Examiner has failed to provide a sufficient evidentiary basis for her factual assumptions relied upon in making this showing.

Therefore, Applicants submit that the rejection of claims 35-45 under 35 U.S.C. Section 101 is improper and should be withdrawn.

Rejection of Claims 52-54, 56-58, 60-63, 65-70 and 72-78 Under 35 U.S.C. Section 112, First Paragraph

Claims 52-54, 56-58, 60-63, 65-70 and 72-78 are rejected under 35 U.S.C. Section 112, first paragraph as not being supported by a specific or substantial or credible asserted utility or a well-established utility. Applicants respectfully traverse this rejection.

Applicants herein incorporate by reference their arguments made above in connection with the 35 U.S.C. Section 101 rejection. Therefore, in view of said arguments, Applicants submit that this rejection is improper and should be withdrawn.

Applicants submit that the claims are now in condition for allowance.

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